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Highly Regioselective Monothionation of Squaric and Semisquaric Acid Derivatives

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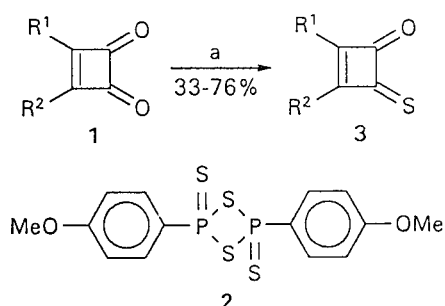
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An efficient synthesis of 4-thioxocyclobut-2-enones by the action of 0.5 molar equivalents of Lawesson's reagent on the corresponding diones is reported.

The chemistry of squaric acid has found considerable interest over the last thirty years.^{1,2} A noteworthy application is the conversion of dialkyl squarates into 3,4-disubstituted cyclobut-3-ene-1,2-diones which allows a plethora of further transformations via vinylketene intermediates.^{3,4} Consequently, analogous transformations from the corresponding vinylthioketenes can be envisaged from 4-thioxocyclobut-2-enones. In fact, a few monothiones with 3-dialkylamino or symmetrical 3,4-bis(dialkylamino) substitution have been reported,⁵⁻⁹ but for the former only indirect evidence on the site of thionation was obtained. Phosphorus pentasulfide appeared to be the sulfur transfer reagent of choice, though it may lead to bithionation. In contrast, ethoxycarbonyl isothiocyanate allows selective monothionation, but works only for 3,4-bis(dialkylamino)cyclobut-3-ene-1,2-diones ("squaric acid diamides").^{7,10} 2,4-Bis(4-methoxyphenyl)-1,3,2,4-dithiadiphosphetane 2,4-disulfide (**2**) ("Lawesson's reagent") which usually allows thionation reactions under mild conditions and in well-defined stoichiometry¹¹ had already proven to be advantageous in the thionation of simple enones¹² calling for its application also in squaric acid chemistry.



(a) 0.5 mol. equiv **2**, CH₂Cl₂, r. t., 12 h

Scheme

Dichloromethane solutions of 4-aryl- or 4-butylsemisquaric acid derivatives **1a-e** or squaric acid derivatives **1f,g** were treated with 0.5 molar equivalents of Lawesson's reagent **2** to yield 4-thioxocyclobut-2-enones **3** in good to moderate yields. The reaction is highly regioselective as neither the regioisomeric monothione nor dithionated products could be detected. Flash chromatography had to be used to separate thiones **3** from phosphorus containing impurities, since excessive base washing resulted in decomposition of **3**. An unambiguous

Table 1. Yields, Physical Properties and IR Spectroscopic Data of 4-Thioxocyclobut-2-enones **3** Prepared^a

| 3 | R ¹ | R ² | Yield (%) | mp (°C) | IR (KBr or neat) ν [C=O, C=C (cm ⁻¹)] |
|----------|------------------------------------|--|-----------|-----------|---|
| a | O <i>i</i> -Pr | Ph | 59 | 144–145 | 1770, 1605 |
| b | O <i>i</i> -Pr | Bu | 76 | oil | 1785, 1605 |
| c | O <i>i</i> -Pr | 4-MeOC ₆ H ₄ | 47 | 139–140 | 1765, 1603 |
| d | O <i>i</i> -Pr | 4-Me ₂ NC ₆ H ₄ | 33 | 146 (dec) | 1760, 1598 |
| e | NET ₂ | Ph | 76 | 95 | 1770, 1642 |
| f | NBn ₂ | OEt | 65 | 80 | 1760, 1640 |
| g | N(CH ₂) ₂ O | OEt | 49 | 210 | 1770, 1660 |

^a Satisfactory microanalyses obtained for **3a, c, e-g**: C ± 0.27, H ± 0.11, N ± 0.08, S ± 0.12 except for S in **3f**: + 0.46 (S not measured for **3a, c**); for **3b-e** exact mass with maximum deviation ± 0.0007 (**3d**).

proof of the site of thionation in **1** met with difficulties. Charge control of the reaction should favor attack of the reagent on the carbonyl group of the highly delocalized 3-(amino or alkoxy) enone moiety to give **3** with a vinyllogous thioamide or thionoester unit, but also thionation of nonactivated thiones by **2** is a well-established reaction.¹³ Formation of **3** would be in line with previous claims on the regioselectivity of the reaction,^{5,6,8} but the failure to thionate dialkyl squarates with **2**¹⁰ shed doubt on the thionation of the 3-(isopropoxy) enone moiety in **1a-e**. Moreover, NMR data gave no clue as to the position of the sulfur; in particular, a 2D-COLOC-NMR spectrum of **3b** revealed coupling of the 1-methylene protons of the butyl substituent with both the carbonyl and the thiocarbonyl carbon. Therefore, an X-ray structural investigation of a single crystal of **3a** was carried out and finally confirmed the suggested structure (Figure). Pronounced electron delocalization within the S4-C4-C3-C2-O21 unit is shown by a relatively short C3-C4 distance as compared to the C1-C2 bond (Figure) and also in comparison to the enone moiety in a 3-(ethoxy)cyclobutenone [C=C 1.36 Å, C-C(=O) 1.452 Å].¹⁴ The four-membered ring is planar (maximum deviation 0.1 pm) and the benzene ring adopts an almost coplanar position [angle between planes 3.7(2)°].

Having established structure **3a**, the same regioselectivity is assumed for derivatives **3b-d** and, similarly, also for **3e-g** assuming the preferred thionation of the even more polarized vinyllogous thioamide unit.

NMR spectra were recorded on a Bruker ARX-400 or G. E. Omega 500 spectrometer using CDCl₃ and TMS as internal standard. IR spectra were recorded on a Perkin-Elmer 1600 FT-IR spectrometer.

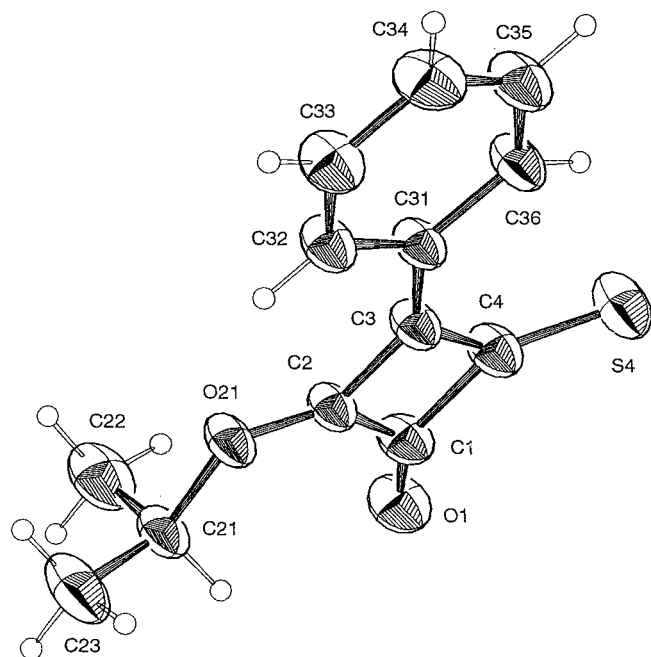


Figure. X-ray structure of **3a** in the ORTEP presentation. Selected bond distances [Å] and bond angles [°]: S4–C4 1.627(3), O1–C1 1.201(4), O21–C2 1.298(3), O21–C21 1.484(3), C1–C2 1.490(4), C1–C4 1.510(4), C2–C3 1.395(4), C3–C31 1.443(4), C3–C4 1.449(4); C2–C1–C4 86.0(2), C3–C2–C1 92.4(2), C2–C3–C4 92.1(2), C3–C4–C1 89.5(2)²²

MS were recorded on a VG Analytic 7070E instrument. Elemental analyses were performed by Pharmazeutisches Institut, TU Braunschweig. Merck silica gel 60 was used for chromatography. THF was distilled from diphenylketyl sodium just prior to use. Solvents for chromatography were distilled prior to use. Diones **1** could be obtained from dialkyl squarates using literature procedures: 3-isopropoxy-4-phenyl- (**1a**),¹⁵ 3-butyl-4-isopropoxy- (**1b**),¹⁶ 3-diethylamino-4-phenyl- (**1e**),² 3-(dibenzylamino)-4-ethoxy- (**1f**),¹⁷ and 3-ethoxy-4-morpholinocyclobut-3-ene-1,2-dione (**1g**).¹⁸ 3-Isopropoxy-4-(4-methoxyphenyl)cyclobut-3-ene-1,2-dione (**1c**) was prepared analogously to ref 15; yield 73%; mp 99–100°C (Lit. 101–102°C). ¹H NMR: δ = 1.54 (d, 6H, J = 6.2 Hz, *i*-Pr-CH₃), 3.88 (s, 3H, OCH₃), 5.59 (sept, 1H, J = 6.2 Hz, *i*-Pr-CH), 7.00, 8.03 (each d, 2H, J = 8.8 Hz, C₆H₄). 3-(4-Dimethylaminophenyl)-4-isopropoxycyclobut-3-ene-1,2-dione (**1d**) was obtained analogously to ref 7; yield 49%; yellow solid; mp 151–152°C. ¹H NMR: δ = 1.52 (d, 6H, J = 6.2 Hz, *i*-Pr-CH₃), 3.09 (s, 6H, NCH₃), 5.57 (sept, 1H, J = 6.2 Hz, *i*-Pr-CH), 6.71, 7.94 (each d, 2H, J = 8.9 Hz, C₆H₄). ¹³C NMR: δ = 23.0 (*i*-Pr-CH₃), 40.0 (NCH₃), 78.8 (*i*-Pr-CH), 111.4, 115.6, 129.9, 153.0 (C₆H₄), 174.1 (C-3), 190.3, 191.1, 193.8 (C-1, C-2, C-4).

Thionation of Cyclobutenediones **1**; General Procedure:

To a solution of **1** (5 mmol) in CH₂Cl₂ (3 mL) was added Lawesson's reagent **2** (1.011 g, 2.5 mmol). The reaction mixture was stirred overnight at r.t. EtOAc (50 mL) was added and the solution was washed with 10% aq NaOH (2 × 10 mL), sat aq NaHCO₃ (10 mL), and brine (2 × 10 mL). The organic layer was dried (MgSO₄), the solvents were removed in vacuo, and the residue was purified by flash chromatography (silica gel, CH₂Cl₂/hexanes 3:2). For yields and properties see Tables 1–3.

Crystal Structure Analysis of **3a**:

Rotating crystal and precession photographs of a crystal with dimensions 0.3 × 0.2 × 0.1 mm gave approximate lattice constants

Table 2. ¹H NMR Spectroscopic Data [(CDCl₃/TMS) δ , J (Hz)] of 4-Thioxocyclobut-2-enones **3** Prepared

| 3 | δ_{2-XCH} | δ_{2-XCCH} | δ_{Ar-H} | Other Signals |
|----------|---------------------------|---------------------------|------------------------------------|--|
| a | 5.59 (sept, J = 6.2) | 1.60 (d, J = 6.2) | 7.49–7.59, 8.42–8.46 (m) | – |
| b | 5.37 (sept, J = 6.2) | 1.49 (d, J = 6.2) | – | 0.93 (t, J = 7.4), 1.38 (qt, J = 7.4), 1.70 (tt, J = 7.4), 2.72 (t, J = 7.4) |
| c | 5.56 (sept, J = 6.2) | 1.59 (d, J = 6.2) | 7.01, 8.43 (each d, J = 9.2) | 3.89 (s) |
| d | 6.33 (sept, J = 6.2) | 1.52 (d, J = 6.2) | 6.70, 7.92 (each d, J = 8.8) | 3.10 (s) |
| e | 3.49, 3.90 (q, J = 7.3) | 1.14, 1.33 (t, J = 7.3) | 7.40–7.49 (m), 7.69 (d, J = 8.4) | – |
| f | 4.48, 4.73 | – | 7.22–7.28, 7.37–7.46 (m) | 1.49 (t, J = 7.2), 5.28 (q, J = 7.2) |
| g | 3.67, 3.83, 3.92 (mc) | – | – | 1.48 (t, J = 7.1), 5.20 (q, J = 7.1) |

Table 3. ¹³C NMR Spectroscopic Data (CDCl₃/TMS, δ) of 4-Thioxocyclobut-2-enones **3** Prepared

| 3 | $\delta_{C=O}$ | $\delta_{C=S}$ | δ_{C-2} | δ_{C-3} | δ_{2-XC} | δ_{2-XCC} | δ_{Ar-C} | Other Signals |
|----------|----------------|----------------|----------------|----------------|-----------------|-------------------|--|--|
| a | 196.8 | 227.6 | 185.2 | 176.2 | 81.4 | 22.8 | 128.0, 128.4, 128.7, 132.9 | – |
| b | 200.6 | 232.4 | 189.2 | 186.6 | 80.3 | 22.6 ^a | – | 13.5, 22.7 ^a , 25.2, 27.2, 55.5 |
| c | 195.7 | 227.8 | 184.9 | 175.8 | 81.2 | 23.0 | 114.3, 121.6, 130.6, 163.4 | 55.5 |
| d | 175.2 | 202.9 | 173.7 | 163.9 | 77.6 | 30.1 | 107.5, 109.9, 123.7, 144.0 | 44.8 |
| e | 185.2 | 217.3 | 180.7 | 171.3 | 45.1, 45.4 | 12.8, 14.4 | 127.5, 128.5, 129.0, 130.2 | – |
| f | 184.3 | 206.9 | 179.9 | 174.7 | 51.7, 52.1 | – | 128.4, 128.8, 128.9, 129.0, 129.2, 129.3, 133.79, 133.82 | 16.3, 70.2 |
| g | 183.9 | 206.6 | 179.6 | 172.7 | 47.6, 47.8 | – | – | 16.3, 66.5, 66.8, 70.0 |

^a Signal assignments may be reversed.

and the preliminary space group. Refinement of the lattice constants led to the following cell dimensions: $a = 8.057(1)$, $b = 9.410(1)$, $c = 9.442(1)$ Å; $\alpha = 92.71(1)^\circ$, $\beta = 113.13(1)^\circ$, $\gamma = 111.76(1)^\circ$; $V = 595.61$ Å³; space group PI ; $Z = 2$; $d_{\text{calcd}} = 1.295$ g cm⁻³. Intensity measurements were carried out with an Enraf-Nonius single-crystal diffractometer CAD 4-SDP using Cu- K_α radiation monochromated with graphite in the θ - 2θ scan technique at ambient temperature. The intensity data were not corrected for absorption. The 2431 measured intensities were reduced to 2258 symmetry-independent reflexions.¹⁹ The structure was solved by the direct-methods program SIR-92.²⁰ The E maps revealed the positions of all the heavy atoms. After the refinement of these positions the H atoms were found from a Fourier synthesis.²¹ In the final refinement, convergence was achieved at $R = 0.0757$.²²

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